Effectiveness of the Q fever vaccine

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Review

Effectiveness of the Q fever vaccine: A meta-analysis

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SUMMARY

In the Netherlands, the number of notified human Q fever cases showed a steep increase over the last three years and is not expected to disappear in the next few years. Since vaccination might be an option to prevent Q fever cases in the general population, evidence is needed about its effectiveness. We therefore conducted a meta-analysis to determine the evidence base for effectiveness for Q fever vaccination in human populations. We calculated Mantel-Haenszel risk ratios and we used the following formula to calculate the vaccines effectiveness: $(1 - \text{mhRR}) \times 100\%$. Although individual and the pooled estimates showed a high effectiveness of Q fever vaccine, conclusions for the general population cannot be confidently drawn about vaccine effectiveness due to potential flaws in the design of the studies and the selected group of study participants.

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1. Introduction

In the Netherlands, the number of notified human Q fever cases, caused by *Coxiella burnetii*, showed a steep increase over the last three years, with 168 versus 2357 new cases in 2007 and 2009 respectively [1]. Despite many measures being taken to prevent further transmission in the Netherlands, it can be expected that Q fever cases will occur in the next few years [1]. This is a serious hazard not only for those at high occupational risk to get the disease, but also to other vulnerable groups, such as pregnant women, immunocompromised persons and those with pre-existing cardiac valve- or vessel-defects [2].

Currently only one Q fever vaccine (Q-Vax, Commonwealth Serum Laboratories Limited) is available for humans. This vaccine is registered in Australia and is there used in the population that has the highest occupational risk (mainly abattoir workers). Since vaccination with Q fever vaccine might be an option to prevent symptomatic and asymptomatic cases of Q fever in the general population, evidence is needed about its effectiveness. In 2007, a paper discussing the effectiveness of human Q fever vaccine was published [3]. However, although this study gave a good overview of literature, it did not aim to conduct a systematic analysis of current evidence for Q fever vaccine effectiveness.

We therefore conducted a meta-analysis to determine the evidence for the effectiveness of Q fever vaccination in humans in a systematic way. Furthermore, as studies on the effectiveness of Q fever vaccination were often small and probably biased, we aimed

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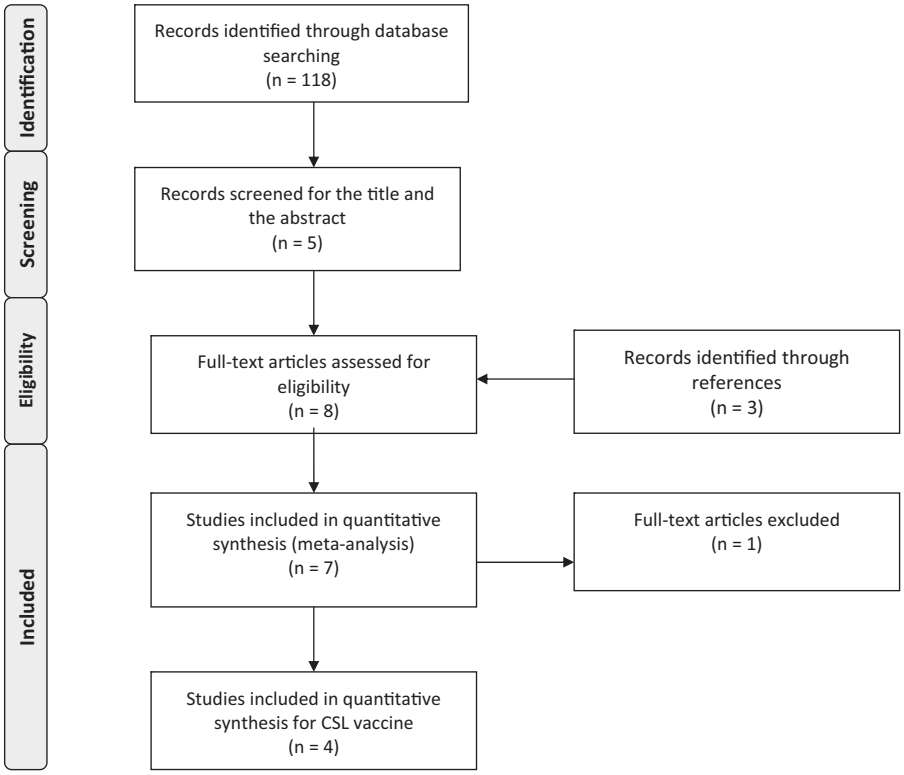

Fig. 1. Flow diagram.

to assess bias by using the assessment criteria for randomized controlled trials and observational studies.

2. Methods

A review of literature was done by searching PubMed and the references of included papers. Our search was limited to human studies in the English language. The search strategy was: ((Q fever OR *Coxiella burnetti* OR *C. burnetti*) AND (vaccination OR vaccine OR immunized OR immunisation)). First we pre-screened the titles and the abstracts; afterwards the eligibility of the studies was judged by reading the full-text. Only the studies that used Q fever vaccine in human and gave information about the clinical outcome and reported the raw data were included in the analysis. The final analysis was performed on the effectiveness of Q-Vax (CSL Limited) vaccine.

The design and possible limitations of the studies were assessed using criteria for randomized control trials [4] and longitudinal non-randomized observational studies [5]. As the main possible limitations we considered bias because of information, selection or confounding, which may lead to the over- or underestimation of the vaccine effectiveness.

The Mantel-Haenszel risk ratio (mhRR) was calculated after pooling the raw data by using Episheet by Rothman [6,7]. Vaccine effectiveness was calculated by the following formula: $(1 - \text{mhRR}) \times 100\%$.

3. Results

3.1. Results of the search

The first search resulted in more than a hundred hits. Only five articles met our inclusion criteria, and three extra papers were included after screening the references (Fig. 1). We had to exclude one paper [8] that described an interim analysis as we included the complete study in our meta-analysis [9]. Finally, our search resulted in seven studies containing the raw data about the effectiveness of the Q fever vaccine [9–15]. Four of them contained the raw data about the effectiveness of Q-Vax (CSL Limited) [9,10,13,15].

We included three retrospective cohort studies [10,13,14], one prospective cohort study [9], one randomized controlled trial [15] and two experimental studies [11,12]. Except for the volunteers in the experimental studies, the study population consisted of persons who are at risk to get Q fever due to their profession, mostly abattoir workers and laboratory staff.

The summary of the included studies can be found in Table 1.

3.2. Assessment of vaccine effectiveness

All of the studies showed a protective effect of the vaccine against Q fever (ranged between 91 and 100%). The overall effectiveness of the vaccine as calculated after pooling the raw data was 97% (95% confidence interval 94–99%).

The incubation time of Q fever is around 15 days. Therefore, those who developed clinical signs and symptoms of Q fever within 15 days after vaccination could be considered to be vaccinated within the incubation time of a natural infection. After excluding those cases, the vaccine effectiveness increased to 99% (95% confidence interval 96–99.7%).

The effectiveness of Q-Vax (CSL Limited) vaccine was 98% (95% confidence interval 94–99%), and reached 100% after excluding the cases that occurred within 15 days after vaccination.

3.3. Assessment of bias

One of the problems in the reviewed studies was possible bias due to the inclusion and exclusion criteria of vaccinees and nonvaccinees. In six of the reviewed studies the subjects were excluded from receiving Q fever vaccination when they had a positive antibody titre (CF titre >=2.5) and/or positive skin test [9,10,12–15];

Table 1
Description of studies included into meta-analysis.

	Ackland et al. [10]	Benenson [11]	Gilroy et al. [13]	Marmion et al. [9]	[a]Philip [14]	[a]Richard B. Hornick [12,14]	Shapiro et al. [15]
Used Q-fever vaccine and dosage	Q-Vax, CSL (3 batches of 30 μg and 1 batch of 20 μg)	Formalin-killed Ether-extracted Henzerling strain Q-fever vaccine (3 × 1 ml)	Q-Vax, CSL	Q-Vax, CSL (1 × 30 μg)	Q58-A (1 × 22 μg 1ml)	Q-Vax, CSL (1 × 30 μg)	Q-Vax, CSL (1 × 30 μg)
Study design	Retrospective cohort study	Experimental study	Retrospective cohort study	Prospective cohort study	Retrospective cohort study	Experimental study	RCT, double blind, crossover
Intervention for control group	–	–	–	–	–	–	Flu-vax .05 ml
Setting, study population	3 Australian abattoirs, workers	USA, men volunteers	1 Australian abattoir, workers	1 Australian abattoir, workers	Laboratory staff	USA, volunteers	3 Australian abattoirs, workers
Exclusion and inclusion criteria for vaccinees	Exclusion: positive serology (CF titer > = 2.5) or skin test positive (presence of induration at 5–7 days); with a few exceptions	None	Inclusion: negative serology (CF titer < 2.5) and skin test negative (7 days after the test)	Inclusion: negative serology (CF negative at < 2.5) and skin test negative	Inclusion: skin test negative	Inclusion: negative serology	Volunteers; Exclusion: positive serology and skin test positive
Exclusion and inclusion criteria for nonvaccinees	Not given, but most likely both, who have positive and negative markers for Q-fever	None	None	Both; but possibility to see the raw data with the same inclusion criteria as for cases	Inclusion: skin test negative	Inclusion: negative serology	Volunteers; Exclusion: positive serology and skin test positive
Case definition	"The pattern of symptoms and signs conformed to the description of clinical Q-fever" and "serological evidence indicating current or quite recent infection with *C. burnetii*"	"Developing clinical disease"; "showing complement-fixing antibodies"	Confirmed case: > = 4 increase in antibody titer to phase II antigen (AG) by CFT[c] or a positive IgM titer (> = 80) to phase II AG by IFT[d]. Suspected case: At least 4 of the following symptoms: fever, sweats, rigorous, fatigue, headache, myalgia, arthralgia, cough; serological tests negative or not available.	Not given	Not given	Not given	Suspected Q fever cases tested by CFT, IFT
Number of cases among vaccinees	2[e]/2553	2/27	0/19	2[e]/690	0/282	2/83	0/98
Number of cases among nonvaccinees	55/1365	8/10	7/68	7/61	2/37	5/6	7/102
Effectiveness (RR, CI 95%)	98% (92%-99%)	91% (64%-98%)	100%	97% (88%-99%)	100%	97% (88%-99%)	100%
Effectiveness[b]	100%	–	–	100%	–	–	–
Limitations	1. Vague definition of cases	1. Vague definition of cases	1. No description of baseline characteristics of vaccinees and nonvaccinees	1. No case definition	1. Insufficient case definition	1. Insufficient case definition	1. No information about the baseline characteristics
	2. Exceptions in inclusion/exclusion of cases	2. No sufficient description of the baseline characteristics of vaccinees and nonvaccinees		2. The allocation procedure between vaccinees and nonvaccinees not described	2. No information about the baseline characteristics of vaccinees and nonvaccinees	2. No information about the baseline characteristics of vaccinees and nonvaccinees	2. Allocation procedure is not described
	3. No sufficient description of the baseline characteristics of vaccinees and nonvaccinees	3. No randomization or allocation procedures described			3. No thresholds for skin tests	3. Inclusion criteria are not sufficiently described	3. Case definition is not sufficiently described
		4. No pre-vaccination screening					4. Exclusion criteria are not sufficiently described

[a] These studies were described in review papers by Fiset [12] and Ormsbee [14].
[b] After excluding those who got ill within 15 days after receiving Q-fever vaccine.
[c] Complement fixation test.
[d] Immunofluorescence test.[e]Q fever cases occurred within 15 days after vaccination.

however there were exceptions and in some cases the thresholds of serological and/or skin tests were not given [10–12,14]. In three studies the inclusion and exclusion criteria for nonvaccinees were not given or it was different from the criteria used for vaccinees [10,11,13]. The inclusion of skin- and/or seropositive nonvaccinees might have led to underestimation of vaccine effectiveness as persons with positive markers are thought not to be at risk for Q fever infection.

Furthermore, vague or even absent case definition might have led to both under- and overestimation of vaccine effectiveness due to lack of objective assessment. Only in one of the reviewed studies Q fever case definition was properly described and included both a list of clinical symptoms and the cut-off values for serological markers [13]. Three studies also used serological markers to confirm suspected Q fever cases [10,11,15]; however the detailed description, including the list of symptoms and the cut-off points of serological markers was missing. A couple of studies did not provide any case definition. Only one of the reviewed studies was a blinded study [13].

The absence of the description of the baseline characteristics of both vaccinees and nonvaccinees might have led to bias as well. The description of baseline characteristics, such as gender or age, of vaccinees and nonvaccinees was poor or absent in six studies [10–15]. For example, according to the National Q fever management program in Australia, the incidence and vaccination against Q fever is higher in males than in females [16]. There is already some evidence from animal studies that females are less susceptible to Q fever infection than males due to female hormones [17]. Such differences in the distribution of gender between vaccinees and nonvaccinees at baseline therefore might lead to bias. Only one of the reviewed studies provided a sufficient description of baseline characteristics [9].

4. Discussion

Individual studies showed that the effectiveness of the vaccine against Q fever is very high, without exceptions [9–15]. The same high vaccine effectiveness was found after pooling the raw data. Even when cases that occurred within 15 days after vaccination were included, the vaccine effectiveness was very high. However, the designs of the included studies had some potential flaws.

Different inclusion and exclusion criteria for vaccines and nonvaccinees, inclusion of seropositive nonvaccinees, vague or absent Q fever case definition, and differences in baseline characteristics of vaccinees and nonvaccinees might have led to biased results of Q fever vaccine effectiveness.

Another major problem was the selected study sample: there were two studies performed on volunteers, four of the studies focused on abattoir workers and one study focused on laboratory staff. Although information about the demographic characteristics was limited, the study sample was relatively young. At least in three of the reviewed studies the mean age was around 30 years [9,10,13]. Furthermore, the authors of the reviewed studies did not give information about the health status of the study participants. Still, as the study subjects were abattoir workers, laboratory staff and volunteers, it seems likely that they were relatively healthy. This creates problems to generalize the results in different populations. Additionally, it is unclear for how long the vaccine is protective against Q fever, and whether this protection is the result of vaccination in combination with a constant exposure to *Coxiella burnetii*. It was shown that the number of Q fever cases decreased with longer employment at the abattoir [10].

5. Conclusion

In all, the vaccine effectiveness in groups with a high risk for Q fever seems to be very high.

However, due to the selected study population and the absence of a proper description of the studied samples and study procedures, it is not possible to generalize our results and draw conclusion about the effectiveness of Q fever vaccine in the general population or in specific groups of patients. One of the important goals for the future should be decreasing Q fever incidence and prevention of related complications in persons who are not at constant exposure, but might be more vulnerable, such as pregnant women, immunocompromised persons or those with pre-existing cardiac valve- or vessel-defects.

It seems likely that the vaccine against Q fever might decrease the incidence of Q fever in these specific groups and in the general population as well. However more blinded, randomized and unbiased research about its effectiveness is needed.

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References

[1] van der Hoek W, Dijkstra F, Schimmer B, Schneeberger PM, Vellema P, Wijkmans C, et al. Q fever in the Netherlands: an update on the epidemiology and control measures. Euro Surveill 2010;15(12).
[2] Maurin M, Raoult D. Q fever. Clin Microbiol Rev 1999;12(4):518–53. Oct.
[3] Chiu CK, Durrheim DN. A review of the efficacy of human Q fever vaccine registered in Australia. N S W Public Health Bull 2007;18(7-8):133–6. Jul.
[4] Deeks JJ, Higgins JPT, Altman DG. Analysing and presenting results. In: Alderson P, Green S, Higgins J, editors. Cochrane Handbook for systematic reviews of interventions 4. 2. 5; section 8. Chichester, UK: John Wiley & Sons; 2010.
[5] Wells G.A., Shea B., O'Connell D., Peterson J., Welch V., Losos M., et al. The Newcastle-Otawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses; 2010. URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
[6] Rothman JK, Greenland S. Modern epidemiology. 2nd ed.; 1998.
[7] Sato T. Biometrics 1989:1323–4.
[8] Marmion BP, Ormsbee RA, Kyrkou M, Wright J, Worswick DA, Cameron S, et al. Vaccine prophylaxis of abattoir-associated Q fever. Lancet 1984;2(8417-8418):1411–4. Dec 22.
[9] Marmion BP, Ormsbee RA, Kyrkou M, Wright J, Worswick DA, Izzo AA, et al. Vaccine prophylaxis of abattoir-associated Q fever: eight years' experience in Australian abattoirs. Epidemiol Infect 1990;104(2):275–87. Apr.
[10] Ackland JR, Worswick DA, Marmion BP. Vaccine prophylaxis of Q fever. A follow-up study of the efficacy of Q-Vax (CSL) 1985–1990. Med J Aust 1994;160(11):704–8. Jun 6.
[11] Benenson AS. Q fever vaccine: efficacy and present status. In: Smadel JE, editor. Symposium on Q fever ArmyMed Serv Grad School Walter Reed ArmyMed Center Med Sci Publ No 6 U S Government Printing Office. 1959. p. 47–60.
[12] Fiset P. Vaccination against Q fever. In: Proceedings of first international congress on vaccines against viral and rickettsial diseases of man. PAHO Science Publication; 1967. p. 147–528.
[13] Gilroy N, Formica N, Beers M, Egan A, Conaty S, Marmion B, Abattoir-associated. Q fever: a Q fever outbreak during a Q fever vaccination program. Aust N Z J Public Health 2001;25(4):362–7. Aug.
[14] Ormsbee RAMB. Prevention of Coxiella burnetii infection-vaccines and guidelines for those at risk. In: Marrie T, editor. Q fever. Boca Raton, Florida: CRC Press; 1990.
[15] Shapiro RA, Siskind V, Schofield FD, Stallman N, Worswick DA, Marmion BP. A randomized, controlled, double-blind, cross-over, clinical trial of Q fever vaccine in selected Queensland abattoirs. Epidemiol Infect 1990;104(2):267–73. Apr.
[16] Gidding HF, Wallace C, Lawrence GL, McIntyre PB. Australia's national Q fever vaccination program. Vaccine 2009;27(March 23 (14)):2037–41.
[17] Leone M, Honstettre A, Lepidi H, Capo C, Bayard F, Raoult D, et al. Effect of sex on Coxiella burnetii infection: protective role of 17beta-estradiol. J Infect Dis 2004;189(2):339–45. Jan 15.